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EDITORIAL COMMENT

Platelet Reactivity and Percutaneous Coronary Intervention

Another Clue in the Quest for the Holy Grail of Tailored Antithrombotic Therapy?*

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A large investigational effort has been made over the past 30 years in the attempt to identify the optimal antithrombotic therapy for patients undergoing percutaneous coronary intervention (PCI). One of the key messages consistently arising from clinical trials is that the stronger the platelet inhibition at the time of PCI, the lower the incidence of thrombotic events following the procedure (1–4). The periprocedural period is a vulnerable time frame during which the patient's prognosis is mainly delineated. An adequate pre-PCI antiplatelet treatment is required not only to prevent thrombotic complications immediately after the procedure, but also to reduce recurrent ischemic events at follow-up. This is particularly true for patients with acute

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coronary syndrome, where a more pronounced thrombotic milieu is expected and strong platelet inhibition is even more desirable. Using several platelet function tests, the effect of platelet inhibitors, and of thienopyridine clopidogrel in particular, has been extensively studied (5). A large interindividual variability exists in platelet reactivity and response to antiplatelet treatment, the latter being a multifactorial variable influenced by genetic, cellular, and clinical factors (6). As a consequence, following pre-treatment with the recommended 600-mg loading dose of clopidogrel, a considerable proportion of patients undergo PCI with inadequate levels of platelet inhibition (either too high or too low). Whereas patients with increased response to clopidogrel, and therefore low platelet reactivity, are exposed to an increased risk of bleeding complications (7,8), those with high platelet reactivity (HPR) present an increased risk of ischemic complications (9–11). In patients with non–ST-segment elevation myocardial infarction (NSTEMI), HPR detected prior to PCI despite treatment with clopidogrel has been associated with higher rates of periprocedural myonecrosis (12) and 30-day ischemic events including stent thrombosis (13).

In this issue of the *Journal,* Sibbing et al. (14) present the results of a platelet substudy of ISAR-REACT 4 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment). In the main study, the investigators compared the efficacy and safety of bivalirudin versus the combination of abciximab and unfractionated heparin (UFH) in NSTEMI patients undergoing urgent PCI after a 600-mg load of clopidogrel (15). They found that at 30-day follow-up, both treatments were associated with the same incidence of ischemic events (death, recurrent myocardial infarction, target vessel revascularization), whereas bivalirudin resulted in a significant reduction of major bleeding. The investigators conducted this substudy to evaluate whether platelet reactivity, measured after clopidogrel loading and before PCI with the Multiplate analyzer (Verum Diagnostika, Munich, Germany), would influence outcomes regardless of the original randomization allocation. Based on previous evidence (16), HPR was defined as ≥468 arbitrary units (AU) × min, whereas low platelet reactivity was defined as ≤188 AU × min. The results showed that, while in the abciximab-UFH arm efficacy was similar in patients with and without HPR (9.4% vs. 6.7%; odds ratio [OR]: 1.4, 95% confidence interval [CI]: 0.6 to 3.5, $p = 0.43$), in the bivalirudin arm the incidence of ischemic events was significantly higher in patients with HPR (22.0% vs. 5.0%; OR: 5.4, 95% CI: 2.4 to 12.1, $p < 0.0001$), with a significant interaction between treatment arm and platelet reactivity group (p for interaction = 0.037). Intuitively, this shows that a stronger platelet inhibition, such as provided by abciximab, is necessary in NSTEMI patients who still have HPR after pre-treatment with clopidogrel, whereas bivalirudin alone appears to be inadequate in this setting. Potential benefits from glycoprotein IIb/IIIa inhibitors in patients with persistent HPR despite clopidogrel had been previously described by 2 relatively small randomized studies where additional, potent platelet inhibition resulted in better periprocedural outcomes (17,18). The present study further extends this evidence, showing that the use of abciximab is able to mitigate the negative influence of HPR by cutting the incidence of 30-day adverse ischemic events (including large myocardial infarction) to the level of patients without HPR. On the other hand, the results of this study also suggest the lack of protective effect by bivalirudin in patients with HPR, despite the demonstrated antiplatelet effects of this drug. Bivalirudin has been

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shown to suppress thrombin-dependent platelet activation preventing cleavage of protease-activated receptor-1 (19), and to further inhibit adenosine diphosphate–induced platelet aggregation in patients pretreated with clopidogrel (20). However, to date no clear evidence of clinical benefit correlated to this antiplatelet effect of bivalirudin has been provided. In contrast, according to the present results, bivalirudin might not be considered a reasonable option in NSTEMI patients with HPR at the time of PCI if given as the only antithrombotic drug on top of clopidogrel. In fact, when considering only patients with HPR, those treated with bivalirudin presented an incidence of ischemic events at 30 days as high as 22%, more than double compared with that of patients receiving abciximab plus UFH (9.4%).

Although largely underpowered to evaluate hemorrhagic endpoints, it is worth noting that the distribution of major bleeding reflected that observed in the main trial, with higher incidence in patients receiving abciximab plus UFH (1.8% vs. 0.3%). Interestingly, in the latter group, all events except 1 occurred in patients with low platelet reactivity, in keeping with recent evidence that when platelet reactivity is too strongly inhibited, a significantly increased bleeding risk arises (7,8), thereby lending further support to the concept of a therapeutic window of platelet inhibition, which identifies patients with intermediate values of residual platelet reactivity at lower risk for both ischemic and bleeding complications following PCI (16,21).

It is worth remembering that this is a post hoc analysis, investigating only a minority of the entire population of ISAR-REACT 4; furthermore, the risk profile of the patients included in the present substudy is different—and lower—from that of the original population. Taking all of this into account, and bearing in mind that they should be considered with caution, the results of the present study generate an intriguing hypothesis enriching the scenario of tailored antithrombotic strategies for patients undergoing PCI. Although recent trials have failed to demonstrate a benefit from selecting antiplatelet treatment based on platelet function testing in low-risk patients, even when new more potent $P2Y_{12}$ inhibitors were used (22,23), a new paradigm is offered by ISAR-REACT 4 and its platelet substudy. In particular, in NSTEMI patients with normal or low platelet reactivity, bivalirudin could be used during PCI to achieve similar efficacy and a better safety profile compared with abciximab plus UFH, whereas the latter should be reserved for patients with residual HPR despite clopidogrel 600 mg in order to reduce recurrent ischemic events. This hypothesis, and others using newer antiplatelet drugs, need to be tested in further clinical trials. And the quest can go on.

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Key Words: abciximab ■ bivalirudin ■ clopidogrel ■ high platelet reactivity.